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11

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/856,322 | RAMRAKHA ET AL. | |
| | Examiner | Art Unit | |
| | Q. Janice Li | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *17-32* is/are pending in the application.

4a) Of the above claim(s) *19-26,29, 30, 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,18,27,28 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

## DETAILED ACTION

Applicant's election with traverse of Group IV, claims 17, 18, 27, 28, and 31, in Paper No. 9 is acknowledged. Applicants requested traversal of restriction and examining groups IV-VI and X together in this application. The traversal is on the ground(s) that "*groups IV-VI and X represent a web of knowledge and continuity of effort that merits examination in a single application*", that "*claims of group IV are directed to cells that contain the proteins of group V and nucleic acids of group VI, which can be used to generate the animal of group X. Accordingly all of the claims are directed to products that depend on the same inventive feature except for claim 31*". This is not found persuasive. It is maintained that the invention listed as groups IV-VI and X do not relate to a single inventive concept under PCT Rule 13.1, because the inventions are drawn to mutually exclusive and independent products that belong to different chemical entities and have distinct mode of operation. 37 CFR 1.475 (b) states "AN INTERNATIONAL OR A NATIONAL STAGE APPLICATION CONTAINING CLAIMS TO DIFFERENT CATEGORIES OF INVENTION WILL BE CONSIDERED TO HAVE UNITY OF INVENTION **IF** THE CLAIMS ARE DRAWN **ONLY TO ONE** OF THE FOLLOWING COMBINATIONS OF CATEGORIES: (1) A PRODUCT AND A PROCESS SPECIALLY ADAPTED FOR THE MANUFACTURE OF SAID PRODUCT; OR (2) A PRODUCT AND A PROCESS OF USE OF SAID PRODUCT; OR (3) A PRODUCT, A PROCESS SPECIALLY ADAPTED FOR THE MANUFACTURE OF THE SAID PRODUCT, AND A USE OF THE SAID PRODUCT; OR (4) A PROCESS AND AN APPARATUS OR MEANS SPECIFICALLY DESIGNED FOR CARRYING OUT THE SAID PROCESS; OR (5) A PRODUCT, A PROCESS SPECIALLY ADAPTED FOR THE MANUFACTURE OF THE SAID PRODUCT, AND AN

APPARATUS OR MEANS SPECIFICALLY DESIGNED FOR CARRYING OUT THE SAID PROCESS." Since multiple products are claimed, unity of invention is lacking and restriction is required.

Moreover, under PCT Rule 13.2, they lack the same or corresponding special technical features and each of the Inventions requires a separate search status and consideration. For example, as indicated in the International Preliminary Examination Report and this Office action, claims of group IV, but not claims of group X, are anticipated or obvious over *Dorling et al*, *Greenman et al*, and *Klein et al*, therefore, the special technical feature which links group IV and X does not provide a contribution over the prior art as a whole, so unity of invention is lacking.

Therefore, it is maintained that these inventions are distinct due to their divergent subject matter. Further search of these inventions is not co-extensive, as indicated by the separate classifications. The requirement is still deemed proper and is therefore made **FINAL**.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 17-32 are pending, however, claims 19-26, 29, 30, and 32 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim.

Claims 17, 18, 27, 28, and 31 are under current examination.

***Priority***

This application is a 371 of PCT/GB99/03888, filed 11/22/1999, and claims priority to UK 98255557, filed 11/20/98.

***Claim Objections***

Claims 17, 27, 28, and 31 are objected to because of the following informalities:

Claim 17 reads on multiple inventions. Upon election of an invention for examination in this application, the claim should be amended so that it only reads on the elected invention.

Claims 18, 27, 28, and 31 recite a claim number that has been renumbered according to 37 CFR 1.126 in Paper #6. The claims should be amended so that they reflect such change.

Claims 27, 28, and 31 depend from a claim drawn to a non-elected invention. Upon election of an invention for examination in this application, the content and dependency of the claims should be amended so that they read on the elected invention. For the sake of a compact prosecution, these claims would be constructively interpreted as they recited the elected invention.

Claim 31 is objected to because it lacks an article at the beginning of the phrase. MPEP states each claim begins with a capital letter, preferably an article such as "A", "The", etc. See MPEP § 608.01(m).

### *Specification*

The specification contains amino acid sequences (e.g. page 8, line 29; page 9, line 14; page 15, lines 20-21; and page 17, line 6) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because the sequences have not been identified by a sequence identification number, and provided in sequence listing and in a computer readable copy. Applicants are required to check entire application to identify any sequence recitation that is required by the rule but has not yet identified by a sequence identification number. Applicant must provide a paper copy and a computer readable copy of the Sequence Listing and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). A full response to this Office action must include a complete response to the requirement for a new Sequence Listing.

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 17 and 18 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 17 is broadly drawn to a biological tissue comprising endothelial cells, which may be induced to generate a polypeptide that down-regulates the expression of a cell adhesion molecule by the cells. Given the broadest reasonable interpretation, the phrase "may be induced to" is interpreted as "capable of being induced to". Therefore, claim 17 embraces any biological tissue comprising endothelial cells, and thus, reads on a product of nature. Amending the claim to recite "isolated" would overcome this rejection.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17, 18, 27, 28, and 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited

to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the nature of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

Claims 17, 18, 27, and 28 are drawn to a biological tissue comprising endothelial cells, which may be induced to generate a compound that down-regulates the expression of a cell adhesion molecule by the cells, wherein the tissue is situated *in vivo* or *ex vivo*. The specification teaches, "the biological tissue may be any tissue suitable for transplantation to a mammal, and includes collection of cells, and individual tissues and organs" (page 5, lines 5-8). The title of the application is "suppression of xenotransplant rejection". Given the broadest reasonable interpretation, the tissue and organ encompassed by the claims are for use as an allograft or xenograft. With respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. "WHEN A COMPOUND OR COMPOSITION CLAIM IS LIMITED BY A PARTICULAR USE, ENABLEMENT OF THAT CLAIM SHOULD BE EVALUATED BASED ON THAT USE". (MPEP 2164.01c) When analyzing the enablement of the claims, the intended use is to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. "A biological tissue suitable for transplantation" is defined as a graft material for a therapeutic use, to prevent, alleviate organ tissue rejection within an

animal undergo any tissue transplantation including allo- and xeno-transplantation, therefore, will be evaluated by the standard.

With regard to "*down-regulates* the expression of a cell adhesion molecule by the cells" (claim 17), the specification teaches construction of a plasmid vector (pEF/sFv/ER, example 2) encoding a single chain antibody against adhesion molecule, VCAM, fused with a signaling peptide comprising KDEL, operably linked to a promoter (EF1-a), transfecting cultivated porcine endothelial cell line A9 with the vector (example 3), wherein the bi-specific polypeptide targets the VCAM to a sub-cellular location (ER), whereby the *surface* expression of VCAM is reduced in the pEF/sFv/ER transfectants compared to controls (figures 7a & 7b), and whereby the binding of a leukocyte (Jurkat 6) to varying densities of endothelial cells is reduced. While it is true that the surface expression of VCAM is down regulated, the overall expression is not down regulated. Rather, the VCAM is targeted to the ER, not transported to the cell membrane. Accordingly, the disclosure of the specification does not support the claim to generally "down-regulates the expression of an adhesion molecule by a cell".

Moreover, claim 17 is drawn to endothelial cells that may be induced to generate a polypeptide with specific binding affinity for the cell adhesion molecule, the specification provides teachings regarding how the adhesion molecules are down regulated when the endothelial cells are transfected with a polynucleotide expressing a bi-specific polypeptide. However, the specification fails to teach how the adhesion molecules are down regulated when the endothelial cells are transfected with a non-bispecific polypeptide as recited in claim 17, and the specification is silent with regard to

means of inducing endothelial cells to generate a polypeptide other than transfecting the cells with a polynucleotide, therefore, fails to provide an enabling disclosure commensurate with the scope of the claims

The sole utility of the claimed tissue is a pharmaceutical composition suitable for xenotransplantation. The specification provided down-regulated binding between cultivated T cells and transfected endothelial cells in an *ex vivo* setting. However, the specification fails to teach whether the degree of binding reduction is sufficient to suppress a vigorous xeno-rejection response in an animal, in which a small amount of endothelial cells are embedded in a solid organ. In light of the state of the art, the specification fails to support the full scope of the claims.

In view of the state of the art in xenotransplantation, there are still major barriers for successful transplantation as of post-filing dates. *Dorling et al* (IDS/8) teaches using an antibody specifically binds to VCAM for endothelial cell accommodation in culture. They teach "DOWN REGULATION OF VCAM WAS ONLY MANIFEST WHEN SUB-SATURATING DOSES WERE USED", "THE DEPENDENCE ON BOTH TIME AND DOSE OF ANTIBODY APPLIED MIGHT EXPLAIN WHY ACCOMMODATION HAS BEEN DIFFICULT TO ACHIEVE CONSISTENTLY IN *IN VIVO* MODELS OF DISCORDANT XENOTRANSPLANTATION" (abstract). Apparently, the skilled artisan acknowledges that to achieve a down-regulating effect, significant amount of antibodies are required and down-regulation of an adhesion molecule *in vitro* does not correlate well with that of *in vivo*. *Simon et al* (Immunol Today 1999;20:323-30) teach the interactions of cross-species adhesion molecule-ligand pairs is one of the many factors to the success of xenotransplantation, they acknowledges the approach of genetically

modifying vascular endothelial cells to suppress the surface expression of VCAM-1 and teach, "ALTHOUGH THIS APPROACH HOLDS GREAT POTENTIAL, IT IS LIKELY THAT ORGANS DERIVED FROM SUCH ANIMALS WOULD STILL GENERATE POWERFUL IMMUNE RESPONSES IN HUMANS" (right column, page 324), and "THE EFFICACY OF MANY ADHESIVE INTERACTIONS RELEVANT TO XENOGENEIC ORGAN TRANSPLANTATION STILL REMAINS TO BE DETERMINED" (Concluding remarks, page 328). The difficulties taught by *Dorling et al* and *Simon et al* have not been overcome at a post-filing date of instant application. *Game et al* (Wien Klin Wochenschr 2001;113:823-38) detailed different types of allogenic and xenogenic rejection (hyperacute, acute, chronic) and underlying mechanisms involving multiple pathways that lead to the failure of allogenic and xenogenic transplantation, and states, "WHILE MAJOR IMPROVEMENTS HAVE BEEN MADE IN THE PREVENTION AND TREATMENT OF HYPERACUTE AND ACUTE TRANSPLANT REJECTION, MOST GRAFTS WILL SUCCUMB TO CHRONIC REJECTION: THIS REFLECTS THE EXTENT OF OUR KNOWLEDGE OF THE MECHANISMS THAT DRIVE THESE PROCESSES", as for xenotransplantation, "NOVEL APPROACHES HAVE OVERCOME SOME EARLY ANTIBODY MEDIATED REJECTION EVENTS BUT THEN REVEAL A HUGE, INTENSE, ADAPTIVE CELLULAR RESPONSE". The teaching illustrates that a biological tissue suitable for xenotransplantation has not become routine for the state of the art at a post-filing date. Therefore, it is incumbent upon applicants to provide sufficient and enabling disclosure to guide the practice of the invention within the specification. However, the specification fails to teach how to overcome the well-known hurdles in the art, it would have required undue experimentation for the skilled artisan intending to use the biological tissue as allograft or xenograft materials.

Claim 31 is drawn to a method of rendering a tissue or organ suitable for transplantation, comprising expressing a bi-specific polypeptide capable of binding to a cell adhesion molecule and suppressing the surface expression of said molecule in endothelial cells. Given the broadest reasonable interpretation, the claim encompasses both *ex vivo* and *in vivo* methods of delivering any type of nucleic acids by any route of administration, specifically to endothelial cells anywhere in the body, and achieving reliable expression of the polypeptide in the endothelial cells, and down-regulation of the surface expression of a cell adhesion molecule to the extend that a therapeutic effect could be achieved, i.e. suppression of a xenograft rejection. The specification teaches transfecting a layer of cultivated immortalized porcine endothelial cells in vitro, however, the specification fails to teach how to deliver the nucleic acid to an organ, such as a neural tissue, a pancreas, or a cartilage where the endothelial cells are embedded in a solid organ; the specification fails to teach how to deliver the nucleic acids *in vivo* specifically targeting endothelial cells, the route of administration, the type of vectors suitable for targeting endothelial cells, and most importantly, the *in vivo* efficiency of the polypeptide in reducing surface expression of adhesion molecules and thus, the efficacy in suppression of xenotransplant rejection.

The types of the vectors and the route of administration are relevant for enabling the claimed invention because each type of virus has different tissue tropism and each vector system has different efficiency in transducing different types of cells. The natural tropism of adenovirus is to respiratory epithelial cells, and of retrovirus, hematopoietic cells. *Robbins et al* (Pharmcol Ther 1998;80:35-47) teach that each type of vector

system has its unique advantages and limitations, "RETROVIRAL VECTORS CAN PERMANENTLY INTEGRATE INTO THE GENOME OF THE INFECTED CELL, BUT REQUIRE MITOTIC CELL DIVISION FOR TRANSDUCTION. ADENOVIRAL VECTORS CAN EFFICIENTLY DELIVER GENES TO A WIDE VARIETY OF DIVIDING AND NONDIVIDING CELL TYPES, BUT IMMUNE ELIMINATION OF INFECTED CELLS OFTEN LIMITS GENE EXPRESSION IN VIVO. HERPES SIMPLEX VIRUS CAN DELIVER LARGE AMOUNTS OF EXOGENOUS DNA; HOWEVER, CYTOTOXICITY AND MAINTENANCE OF TRANSGENE EXPRESSION REMAIN AS OBSTACLES. AAV ALSO INFECTS MANY NONDIVIDING AND DIVIDING CELL TYPES, BUT HAS LIMITED DNA CAPACITY" (abstract). *Robbins et al* go on to teach that non-viral vectors such as naked DNA and liposomes are inefficient in gene transfer to cell nucleus (Section 2, page 36). Thus, retroviral vectors and DNA-liposome would not be efficient in transducing endothelial cells. In light of the teachings, a specific guidance is necessary for practicing the claimed invention without undue experimentation. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired cells *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, *Deonarain* (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ABILITY TO TARGET A GENE TO A SIGNIFICANT POPULATION OF CELLS AND EXPRESS IT AT ADEQUATE LEVELS FOR A LONG ENOUGH PERIOD OF TIME" (page 53, first paragraph). *Miller et al* (1995, FASEB J., Vol. 9, pages 190-199), acknowledge various vector system available in the art, then teach, "NO SINGLE DELIVERY SYSTEM IS LIKELY TO BE UNIVERSALLY APPROPRIATE, FOR INSTANCE, THE REQUIREMENTS OF GENE THERAPY FOR CYSTIC FIBROSIS ARE GREATLY DIFFERENT FROM THOSE OF CANCER" (1st paragraph, page 190). "ONCE AGAIN, TARGETING AT THE LEVEL OF THE VECTOR HAS NOT YET BEEN PARTICULARLY WELL

DEVELOPED; HENCE, LIPOSOME OR VIRAL-MEDIATED DELIVERY OF THE CFTR BEEN TO AIRWAY EPITHELIAL CELLS OF CF PATIENTS HAS RELIED LARGELY ON THE LOCALIZED DELIVERY OF THE VECTORS DIRECTLY TO THE AFFECTED TISSUES" (1st paragraph, page 198)

Thus, it is evident that at the time of the invention, the gene therapy practitioner, while acknowledging the significant potential of gene therapy, still recognized that such therapy was neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for such therapeutic regimen. Although the instant specification provides a brief review of a potential therapeutic use of the claimed biological tissue and data from ex vivo cell studies, it is not enabled for its full scope because the specification fails to disclose any significant gene transfer in any target cells *in vivo*, or any therapeutic effects *in vivo*. In summary, the teachings and guidance presented in the specification, as a whole, represent an initial investigation into the feasibility of the development of a useful means for executing gene therapy that awaits further development to the practical level.

Claim 31 provides a method for down-regulating the expression of a cell adhesion molecule by expressing a bi-specific fusion polypeptide in an endothelial cell. The specification teaches that the binding region of the bi-specific polypeptide binds to a VCAM, whereas the signaling region of the bi-specific polypeptide will target the VCAM to an intracellular location, particularly the endoplasmic reticulum, so that the produced VCAM would stay in a subcellular location rather than transported to the cell surface. In light of the teaching, the bi-specific polypeptide would not down-regulate the expression

of a cell adhesion molecule, rather it suppresses the surface expression of the molecule. Thus, the specification does not appear to provide a sufficient guidance to what is now claimed.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving *in vivo* targeting and expression of a bi-specific polypeptide in endothelial cells in an inducible manner, particularly for suppression of allo- and xeno-transplantation of a biological tissue, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to *in vivo* gene therapy of transplant rejection, and the breadth of the claims directed to the use of numerous therapeutic genes/vectors/expression regulatory elements combinations, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Please note that the rejection under this section is based of the evaluation of the intended use of the claims, therefore, they are not conflicting with the rejection under 35 USC §102 or 103.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17, 18, and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 is vague and indefinite because of the claim recitation, "endothelial cells which may be induced to generate a polypeptide". The specification teaches transducing endothelial cells with a vector comprising an inducible promoter, however, the specification fails to teach other means of inducing an endothelial cell to generate a polypeptide with specific binding affinity for a cell adhesion molecule. Therefore, the metes and bounds of the claim are unclear.

Claim 31 is vague and indefinite because it is incomplete. The claim provides a method comprising expressing a polypeptide in an endothelial cells any where in the body of an animal, however, it is unclear how the goal of the method is achieved. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 17 is rejected under 35 U.S.C. 102(b) as being anticipated by *Klein et al* ((Eur J Cell Bio 1997;72(S43):101)).

Claim 17 is drawn to a biological tissue comprising endothelial cells which may be induced to generate a polypeptide. Given the broadest reasonable interpretation, the phrase "may be induced to" is interpreted as "capable of being induced to". The specification teaches that the term "biological tissue" encompasses "collection of cells" (lines 5-8, page 5).

*Klein et al* teach different endothelial cell lines, which may be induced to generate a polypeptide that down regulates a cell adhesion molecule. Therefore, Klein et al anticipate the instant claims.

Claim 17 is rejected under 35 U.S.C. 102(b) as being anticipated by *Orosz et al* (Transplant 1993; 56:453-60, IDS/2).

*Orosz et al* teach a cardiac tissue comprising endothelial cells (fig. 1), which may be induced to generate a polypeptide that down regulates a cell adhesion molecule. Therefore, *Orosz* et al anticipate the instant claims.

Claims 27 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by *Greenman et al* (J Immunol Meth 1996;194:169-180, IDS/21).

Claim 27 is drawn to a cell comprising a polynucleotide encoding a polypeptide comprising a binding region to a cell adhesion molecule and a signaling region for subcellular targeting of the polypeptide. Claim 28 is drawn to a biological tissue comprising the cell of claim 27, and the specification defines the term "biological tissue" as a collection of cells and individual organ (Specification, page 5, lines 5-8).

*Greenman et al* teach CHO cells (collection of cells) transfected with a polynucleotide encoding a fusion polypeptide comprising a single-chain antibody fragment with specific binding affinity for CD2 (a cell adhesion molecule), and a signaling region for subcellular targeting (NSEKDEL, right column, page 171), Therefore, *Greenman* et al anticipate the instant claims.

Claims 27 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by *Yuan et al* (Biochem J 1996;318:591-6, IDS/23).

*Yuan et al* teach RD and Jukat cells (collection of cells) transduced with a polynucleotide encoding a fusion polypeptide comprising a single-chain antibody fragment with specific binding affinity for VLA-4 (a cell adhesion molecule), and a signaling region for subcellular targeting (KDEL, fig. 1). Therefore, *Yuan* et al anticipate the instant claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17, 18, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Greenman et al* (J Immunol Meth 1996;194:169-180, IDS/21), in view of *Klein et al* ((Eur J Cell Bio 1997;72(S43):101)).

Claims 17 and 18 are drawn to a biological tissue comprising endothelial cells which may be induced to generate a polypeptide that down-regulates the expression of a cell adhesion molecule by specifically binding to the cell adhesion molecule, preferably the polypeptide is a bispecific fusion protein comprising a binding region capable of binding to a cell adhesion molecule and a signaling region for subcellular targeting. Claim 31 is drawn to a method comprising expressing the recited bi-specific polypeptide in endothelial cells, thereby down-regulating the expression of a cell adhesion molecule by the endothelial cell.

*Greenman et al* teach a method comprising expressing a fusion polypeptide in CHO cell, wherein the fusion polypeptide comprising a single-chain antibody fragment with specific binding affinity for CD2 (a cell adhesion molecule), and a signaling region for subcellular targeting (NSEKDEL, right column, page 171), whereby, the expression of cell surface molecules was inhibited (e.g. table 2). They go on to teach that the general approach of intracellular single chain antibody expression provides a simple, efficient way of studying the function of molecules that can not be studied by current techniques such as transgenic or knockout mice, because molecules of interest can be deleted in a controlled manner without genetic modification, that the skilled artisans

have used this approach in various cell types of human, yeast, and xenopus (page 170). *Greenman et al* do not express the polypeptide in endothelial cells.

However, before the effective filing date of instant application, *Klein et al* teach that various cultivated endothelial cells (HUVEC, HAFEC, WBC-EC) are available for investigating the surface expression of adhesion molecules (VCAM-1, ICAM-1).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Greenman et al* by simply substituting the CHO cell with endothelial cells as taught by *Klein et al* and obtaining a collection of endothelial cells with reduced surface expression of a cell adhesion molecule with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention for the cell type of interests and molecules of interests because the method provides a simple and efficient technique for studying the function of molecules in a particular cell type. Thus, the claimed invention as a whole was clearly *prima facie* obvious in the absence of evidence to the contrary.

Please note that intended use limitations bear little weight on the determination of novelty of the invention. In this case, the limitation "rendering a tissue or organ suitable for transplantation" does not carry patentable weight in the determination of anticipation for the claimed products and method. This is because a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Claims 17, 18, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Yuan et al* (Biochem J 1996;318:591-6, IDS/23), in view of *Dorling et al* (Transplant 1996;62:1127-36, IDS/8).

*Yuan et al* teach a method comprising expressing a fusion polypeptide in RD and Jukat cells (T cells), wherein the fusion polypeptide comprising a single-chain antibody fragment with specific binding affinity for VLA-4 (a cell adhesion molecule, the counterpart of VCAM in endothelial cells), and a signaling region for subcellular targeting (KDEL, fig. 1), whereby, the expression of the cell surface molecules was reduced (e.g. table 1), and the T cell adhesion function was impaired (fig. 4). They go on to teach that the general approach of intracellular single chain antibody expression have been used for studying the function of different molecules in different types of cells (right column, page 591). *Yuan et al* do not express the polypeptide in endothelial cells.

However, before the effective filing date of instant application, *Dorling et al* teach that immortalized porcine endothelial cells are available for investigating the surface expression of adhesion molecules (VCAM-1), because VCAM expression in vascular endothelial cells play an important role in xenotransplantation.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Yuan et al,* applying the same strategy of reducing VLA-4 expression in T cells to reducing VCAM expression in endothelial cells as taught by *Dorling et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention for the cell type of interests and molecules of interests, because the method is

apparently a general technique used in different disciplines of biology for studying the function of molecules in a particular cell type. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
March 10, 2003

| Notice to Comply | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09856322 | Ramrakha et al. | |
| | Examiner | Art Unit | |
| | Q. Janice Li | 1632 | |

## NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: See Office action paper No. 10, page 5.

### Applicant Must Provide:

☒ A substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ A substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

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